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Original Article

Association and discriminative performance of TNF-α and CA125 for disease severity and pain severity in endometriosis patients

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Abstract

Endometriosis is a chronic inflammatory disease frequently associated with pelvic pain and disease progression. Tumor necrosis factor-alpha (TNF-α) and cancer antigen 125 (CA125) have been proposed as potential biomarkers reflecting inflammatory activity and disease burden. However, evidence remains limited on whether these biomarkers are associated with both anatomical disease severity and pain severity, particularly among patients with histopathologically confirmed endometriosis. The aim of this study was to evaluate the associations and discriminative performance of TNF-α and CA125 in relation to endometriosis severity and pain severity. A cross-sectional study was conducted at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from October 2025 to January 2026, in which women with histopathologically confirmed endometriosis were included. Disease severity was classified intraoperatively using the revised American Society for Reproductive Medicine (rASRM) system. Pain severity was assessed using the Numeric Rating Scale (NRS). Peritoneal fluid TNF-α was measured using enzyme-linked immunosorbent assay (ELISA), and serum CA125 was measured using electrochemiluminescence immunoassay (ECLIA). Associations were analyzed using Spearman correlation, and discriminative ability was assessed using receiver operating characteristic (ROC) curve analysis. CA125 showed a significant positive correlation with rASRM stage (r=0.401; p=0.005) and TNF-α showed no significant correlation (r=0.068; p=0.649). ROC analysis demonstrated that CA125 had good discriminative ability for disease severity (AUC=0.808; p<0.001) with an optimal cut-off value of 32 U/mL. For pain severity, both CA125 (r=0.344; p=0.018) and TNF-α (r=0.338; p=0.020) had weak but significant positive correlations with NRS scores. ROC analysis indicated fair discriminative ability of CA125 (AUC=0.700; p=0.010) and TNF-α (AUC=0.674; p=0.031) for severe pain, with optimal cut-off values of 50.85 U/mL and 0.023 pg/mL, respectively. These findings highlight that CA125 is more consistently associated with endometriosis severity than TNF-α, while both biomarkers show limited ability to discriminate pain severity.

Keywords: Endometriosis, TNF-α, CA125, disease severity, pelvic pain

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Introduction

Endometriosis is a chronic inflammatory gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, with lesion development and progression driven by estrogen-dependent mechanisms [1,2]. The disease affects approximately 6–10% of women of reproductive age and up to 50% of women with infertility, representing a substantial global health burden among reproductive-aged women [2]. Although some patients remain asymptomatic, endometriosis commonly presents with chronic pelvic pain and infertility, which significantly impair quality of life and psychosocial well-being [2,3].

The pathogenesis of endometriosis involves complex immune dysregulation and chronic inflammation, leading to increased activation of immune cells, particularly macrophages, and subsequent release of inflammatory mediators such as tumor necrosis factor-α (TNF-α) [4]. TNF-α is a key pro-inflammatory cytokine implicated in endometriosis progression through stimulation of ectopic endometrial cell proliferation and modulation of the inflammatory microenvironment [5]. Previous studies have demonstrated elevated TNF-α levels in patients with endometriosis, suggesting its potential utility as a biomarker for disease detection and assessment [6,7]. In addition, cancer antigen 125 (CA125), a glycoprotein biomarker commonly used in the evaluation of pelvic masses [8], has been reported to be increased in patients with endometriosis compared with healthy individuals and has been investigated as a potential marker of endometriosis burden [6,9,10]. Studies have proposed different CA125 cut-off values for supporting endometriosis diagnosis, although its clinical utility remains limited [11,12].

Laparoscopy with histological confirmation remains the gold standard for diagnosing and staging endometriosis; however, its invasive nature highlights the need for reliable non-invasive biomarkers for disease assessment [6]. Although inflammatory cytokines and serum markers have shown potential in endometriosis evaluation, their association with both anatomical disease severity and symptom severity remains incompletely understood. Furthermore, endometriosis-associated pain is a major determinant of impaired quality of life [13], and identifying biomarkers associated with pain severity may provide additional insight into the clinical heterogeneity of the disease. Therefore, the aim of this study was to evaluate the associations and discriminative ability of TNF-α and CA125 levels with disease severity and pain severity in patients with endometriosis.

Methods

Study design, setting and sampling

A cross-sectional study was conducted at the Obstetrics and Gynecology Department of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from October 2025 to January 2026. The required sample size was calculated using the formula for a numerical correlation study based on the Lemeshow method, with a 95% confidence level, 80% statistical power, and an expected correlation coefficient of 0.404, yielding a minimum sample size of 47 patients.

Patients and criteria

This study included women with suspected endometriosis or endometriotic cysts based on clinical examination and transvaginal ultrasonography who were scheduled to undergo laparoscopy or laparotomy. Only patients with histopathologically confirmed endometriosis were included in the final analysis. Patients were required to undergo TNF-α and CA125 examinations, have no history of previous laparotomy or cesarean section and have not received hormonal therapy. Patients with suspected pelvic inflammatory disease or peritoneal tuberculosis based on clinical, laboratory, and ultrasonographic findings, suspected malignancy based on clinical evaluation, laboratory examination, or imaging findings, or other chronic inflammatory conditions that could affect biomarker levels were excluded.

Data collection

Patient demographic and clinical characteristics were recorded at baseline, including age, age at menarche, age at marriage, marital status, obstetric status, occupation, ethnicity, and education

level. Venous blood samples were collected before surgery as part of the clinical evaluation of patients with suspected endometriosis. The timing of blood collection in relation to the menstrual cycle was recorded when available. Serum CA125 levels were measured using an electrochemiluminescence immunoassay (ECLIA) on a Cobas e601 analyzer (Roche Diagnostics, Mannheim, Germany). During laparoscopy or laparotomy, peritoneal fluid samples were collected intraoperatively before irrigation or extensive surgical manipulation. The timing of peritoneal fluid collection in relation to the menstrual cycle was also recorded when available. Peritoneal fluid TNF-α levels were measured using the Quantikine HS ELISA Human TNF-α Immunoassay kit (R&D Systems, Inc., Minneapolis, MN, USA) according to the manufacturer's protocol. Absorbance was measured using a Microplate Reader model 680 (Bio-Rad Laboratories Inc., CA, USA), and data were analyzed using Microplate Manager software version 5.2.1 (Bio-Rad Laboratories Inc., CA, USA). Intraoperative findings were documented for assessment of endometriosis severity based on the revised American Society for Reproductive Medicine (rASRM) classification. Pain severity was assessed before surgery using the Numeric Rating Scale (NRS). Missing data were checked before analysis; participants with missing values for the main biomarker or outcome variables were excluded from the relevant analysis, and no imputation was performed.

Study variables

The dependent variables of this study were disease severity and pain severity, while the independent variables were peritoneal fluid TNF-α and serum CA125 levels. Disease severity was assessed intraoperatively according to rASRM classification and recorded as stages I–IV [14]. Pain severity was evaluated using the NRS, ranging from 0 to 10, where higher scores indicated greater pain intensity, and was categorized as mild-to-moderate pain (NRS <7) and severe pain (NRS ≥7). TNF-α levels were expressed in pg/mL, while CA125 levels were expressed in U/mL.

Statistical analysis

Categorical variables were presented as frequencies and percentages, while continuous variables were presented as median and range (minimum–maximum), according to data distribution. The normality of continuous variables was assessed using the Shapiro–Wilk test. The association of TNF-α and CA125 levels with disease severity and pain severity was analyzed using Pearson's or Spearman's correlation test according to data distribution. The strength of correlation was interpreted based on the correlation coefficient (r). The discriminative ability of TNF-α and CA125 for disease severity and pain severity was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) with 95% confidence intervals (CIs) was calculated. Optimal cut-off values were determined using the Youden Index. The classification performance at the optimal cut-off values was assessed based on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. A $p<0.05$ was considered statistically significant. Data were analyzed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of patients

A total of 47 women with endometriosis were included in this study, and the baseline characteristics and clinical features are presented in **Table 1**. The majority of patients were aged >35 years (55.3%) and were married (89.4%). More than half of the patients had secondary education (53.2%), while nearly two-thirds were nulliparous (66.0%). All patients experienced dysmenorrhea (100%), while the vast majority reported dyspareunia (89.4%) and approximately three-quarters had infertility (72.3%). All patients presented with advanced-stage endometriosis, consisting of stage III (17.0%) and stage IV (83.0%) disease. No patients with stage I or II endometriosis were identified in this study population. The median NRS pain score was 6 (range: 4–8). Mild-to-moderate pain (NRS <7) was observed in 26 patients (55.3%), while severe pain (NRS ≥7) was present in 21 patients (44.7%), with NRS 6 and 7 being the most frequent individual scores. Median TNF-α concentration was 0.022 pg/mL (range: 0.022–2.119), while CA125

concentration was 53.9 U/mL (range: 9.6–164), with both biomarkers showing non-normal distribution (p<0.001) (**Table 1**).

Table 1. Demographic and clinical characteristics of patients with endometriosis (n=47)

Characteristics	Frequency (%)
Age (years)	
20–35	21 (44.7)
>35	26 (55.3)
Marital status	
Married	42 (89.4)
Unmarried	5 (10.6)
Education level	
Primary	2 (4.3)
Secondary	25 (53.2)
Higher education	20 (42.6)
Parity	
Nulliparous	31 (66.0)
Primiparous	3 (6.4)
Multiparous	13 (27.6)
Clinical symptoms	
Dysmenorrhea	47 (100.0)
Dyspareunia	42 (89.4)
Infertility	34 (72.3)
Endometriosis severity (rASRM stage)	
Stage I	0 (0.0)
Stage II	0 (0.0)
Stage III	8 (17.0)
Stage IV	39 (83.0)
Numeric Rating Scale (NRS) pain score	
4	1 (2.1)
5	4 (8.5)
6	21 (44.7)
7	20 (42.6)
8	1 (2.1)
Tumor necrosis factor-α (TNF-α) (pg/mL), median (min–max)	0.022 (0.022–2.119)
Cancer antigen 125 (CA125) (U/mL), median (min–max)	53.9 (9.6–164)

Association between biomarkers and endometriosis severity

Correlation analysis between biomarkers and endometriosis severity is presented in **Table 2**. Since only stage III and stage IV disease were observed in the study population, the observed association reflects differences in biomarker concentrations between these two severity categories. TNF-α did not demonstrate a significant correlation with disease severity (r=0.068; p=0.649). In contrast, CA125 showed a significant positive correlation with disease severity (r=0.401; p=0.005), indicating that higher CA125 levels were associated with more advanced rASRM stage (**Table 2**).

Table 2. Correlation between the levels of tumor necrosis factor-α (TNF-α) and cancer antigen 125 (CA125) with endometriosis severity

Biomarker	Correlation coefficient (r)	p-value
Tumor necrosis factor-α	0.068	0.649
Cancer antigen 125	0.401	0.005

Discriminative ability and classification performance of CA125 for endometriosis severity

The ROC analysis of CA125 for differentiating stage IV from stage III endometriosis was conducted. CA125 demonstrated significant discriminatory ability, with an AUC of 0.808 (95%CI: 0.638–0.977; p<0.001), indicating good performance in distinguishing higher rASRM stage severity (**Figure 1**).

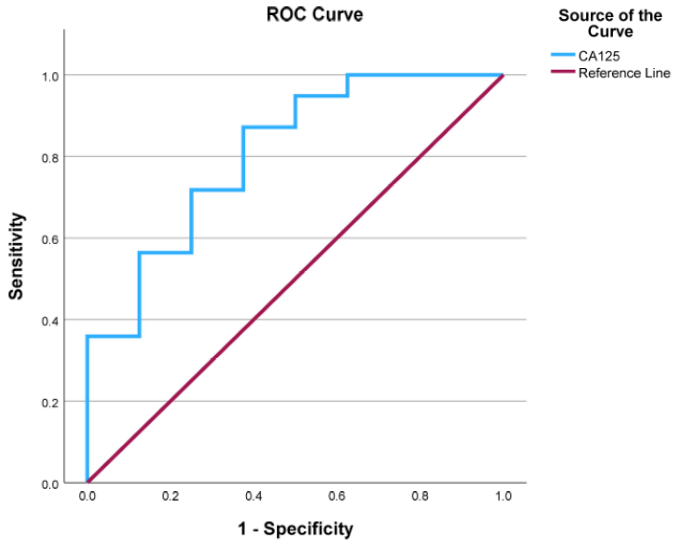

Figure 1. Receiver operating characteristic (ROC) curve of cancer antigen 125 (CA125) for endometriosis severity.

Optimal cut-off value and classification performance of CA125 for differentiating stage IV from stage III endometriosis are presented in **Table 3**. CA125 demonstrated an optimal cut-off value of 32 U/mL for discriminating stage IV from stage III endometriosis, with a sensitivity of 87.2% and specificity of 62.5%. At this threshold, the PPV, NPV, and accuracy were 91.9%, 50.0%, and 83.0%, respectively (**Table 3**).

Table 3. Optimal cut-off values and classification performance of cancer antigen 125 (CA125) for endometriosis severity

Biomarker	Cut-off (U/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Cancer antigen 125	32.0	87.2	62.5	91.9	50.0	83.0

NPV: negative predictive value; PPV: positive predictive value

Association between biomarkers and pain severity

Correlation analysis between biomarkers and pain severity is presented in **Table 4**. TNF-α showed a significant positive correlation with pain severity (r=0.338; p=0.020). Similarly, CA125 demonstrated a significant positive correlation with pain severity (r=0.344; p=0.018), indicating that higher biomarker levels were associated with increased pain severity (**Table 4**).

Table 4. Correlation between the levels of tumor necrosis factor-α (TNF-α) and cancer antigen 125 (CA125) with pain severity in endometriosis

Biomarker	Correlation coefficient (r)	*p*-value
Tumor necrosis factor-α	0.338	0.020
Cancer antigen 125	0.344	0.018

Discriminative ability and classification performance of biomarkers for pain severity

ROC analysis of biomarkers for differentiating severe pain (NRS ≥7) from mild-to-moderate pain (NRS <7) is presented in **Table 5**. TNF-α demonstrated significant discriminative ability, with an AUC of 0.674 (95%CI: 0.515–0.833; p=0.031), indicating fair performance in distinguishing pain severity levels. CA125 showed slightly higher performance, with an AUC of 0.700 (95%CI: 0.549–0.851; p=0.010) (**Figure 2**).

Table 5. Receiver operating characteristic (ROC) analysis of biomarkers for pain severity in endometriosis

Biomarker	Area under the curve	Standard error	95% confidence interval	*p*-value
Tumor necrosis factor-α	0.674	0.081	0.515–0.833	0.031
Cancer antigen 125	0.700	0.077	0.549–0.851	0.010

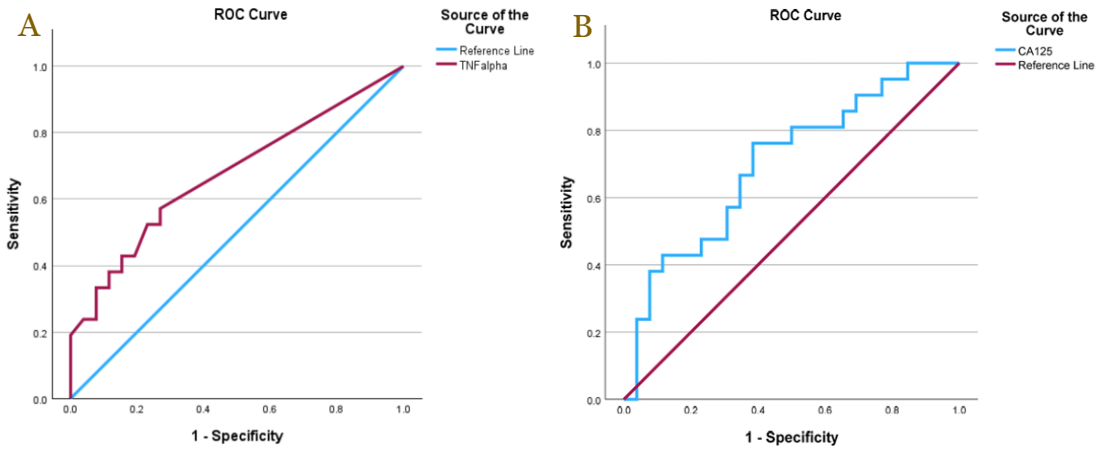

Figure 2. Receiver operating characteristic (ROC) curves of biomarkers, (A) tumor necrosis factor-α (TNF-α) and (B) cancer antigen 125 (CA125), for pain severity.

Optimal cut-off values determined using the Youden Index for discriminating severe pain (NRS ≥7) from mild-to-moderate pain (NRS <7) are presented in **Table 6**. TNF-α demonstrated an optimal cut-off value of 0.023 pg/mL for discriminating severe pain, with a sensitivity of 57.1% and specificity of 73.1%. CA125 showed an optimal cut-off value of 50.85 U/mL, with a sensitivity of 76.2% and specificity of 61.5% (**Table 6**).

Table 6. Optimal cut-off values and classification performance of biomarkers for pain severity

Biomarker	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TNF-α	0.023 pg/mL	57.1	73.1	63.2	67.9	66.0
CA125	50.85 U/mL	76.2	61.5	61.5	76.2	68.0

CA125: cancer antigen 125; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating characteristic; TNF-α: tumor necrosis factor-alpha

Discussion

This study evaluated the association and discriminative ability of TNF-α and CA125 in relation to endometriosis severity and pain severity. CA125 demonstrated a significant positive association with rASRM stage and showed good discriminative ability for differentiating stage IV from stage III disease. In contrast, TNF-α was not significantly associated with rASRM stage. Regarding pain severity, both TNF-α and CA125 showed weak but significant positive associations with pain severity; however, their classification performance for severe pain remained limited.

TNF-α is a key pro-inflammatory cytokine involved in endometriosis pathogenesis through immune activation, macrophage recruitment, and inflammatory signaling [5]. However, this study found no significant association between TNF-α concentration and rASRM stage. This finding is consistent with previous studies reporting that TNF-α levels do not reliably differentiate endometriosis severity, with one study demonstrating no significant difference between early and advanced disease and another showing only a non-significant increasing trend with greater disease severity [15,16]. These findings suggest that although TNF-α contributes to inflammatory processes in endometriosis, its concentration may not directly reflect anatomical disease extent. Cytokine levels can vary according to immune response, lesion activity, menstrual cycle phase, and sampling characteristics. A recent systematic review also reported inconsistent findings regarding the association between TNF-α and endometriosis severity, limiting its application as an isolated marker of disease severity [17]. Furthermore, TNF-α elevation is not specific to endometriosis and may also occur in other inflammatory gynecological conditions [16,18].

Although TNF-α was not associated with rASRM stage, it demonstrated a significant association with pain severity. This finding may be explained by the role of TNF-α in neuroinflammatory pathways involved in pain generation [19,20]. Previous studies have demonstrated that TNF-α activates inflammatory signaling pathways, including NF-κB, MAPK, and ERK, resulting in increased expression of pain-related mediators such as IL-1β, IL-6, IL-8, cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE2) [21,22]. TNF-α may also contribute to

peripheral sensitization through activation of nociceptive pathways involving TRPV1 and p38 MAPK signaling [23]. However, the limited discriminative ability of TNF-α for severe pain classification (AUC=0.674) in this study indicates that TNF-α concentration alone is insufficient to distinguish patients with severe pain from those with mild-to-moderate pain. This finding aligns with previous evidence that endometriosis-associated pain involves multiple factors, including inflammatory mediators, neural involvement, adhesions, hormonal influences, and individual pain perception [24].

In contrast, CA125 demonstrated a significant association with rASRM stage and showed the strongest discriminative ability among the evaluated biomarkers. CA125 is a glycoprotein derived from MUC16 and expressed by coelomic epithelium, which increases in response to peritoneal irritation and chronic inflammation associated with endometriotic lesions [8]. Higher CA125 concentrations may reflect greater lesion burden, peritoneal involvement, and inflammatory activity. Previous studies have demonstrated higher CA125 concentrations in patients with more advanced endometriosis, with significantly elevated levels reported in stage III–IV compared with earlier-stage disease [25,26]. Furthermore, a study evaluating multiple biomarkers identified CA125 as one of the most consistent markers associated with more extensive endometriosis [27].

In this study, CA125 demonstrated good discriminative ability for differentiating stage IV from stage III disease (AUC=0.808), with an optimal cut-off value of 32 U/mL. Previous studies have reported comparable cut-off values [28,29]. A study reported a CA125 cut-off value of 32.45 U/mL with similar sensitivity and specificity findings [28]. Another study demonstrated that CA125 increased with disease severity but had limited ability to identify early-stage disease, supporting its role as a marker of disease burden rather than a screening biomarker for all stages of endometriosis [29]. Therefore, within the current study population consisting exclusively of stage III and IV disease, CA125 demonstrated potential utility in distinguishing greater anatomical severity.

CA125 was also significantly associated with pain severity in this study, although the correlation was weak. This relationship may reflect the association between CA125 and inflammatory burden rather than a direct role in pain transmission. Increased CA125 concentrations may indicate greater peritoneal inflammation and lesion extent, which can contribute indirectly to pain development. Previous studies have reported an association between CA125 concentrations and pelvic pain symptoms, with one study demonstrating improvement in pelvic pain following reduction of CA125 after hormonal treatment and another reporting higher CA125 levels among patients with dysmenorrhea [30,31]. However, a study reported no significant relationship between CA125 concentrations and pain characteristics, suggesting that CA125 alone may not fully represent the complexity of endometriosis-associated pain [32].

This study has some limitations that need to be discussed. The relatively small sample size and single-center design may limit the generalizability of the results to broader endometriosis populations. All included patients had advanced-stage endometriosis, and the absence of stage I–II disease prevented assessment of biomarker performance across the full spectrum of disease severity. Therefore, the observed discriminative ability of CA125 reflects differentiation between stage III and stage IV disease rather than discrimination between early- and advanced-stage endometriosis. The lack of a non-endometriosis control group also limited the ability to determine whether TNF-α and CA125 levels were specifically elevated in endometriosis compared with other gynecological or inflammatory conditions. Biomarker concentrations may have been influenced by biological and clinical factors, including menstrual cycle phase, lesion activity, inflammatory status, and disease phenotype, which were not fully controlled in the analysis. Pain severity was assessed using the NRS, which is subjective and may be affected by individual pain perception, central sensitization, psychological factors, and chronic pain adaptation. In addition, the cross-sectional design precluded assessment of temporal or causal relationships between biomarker levels, disease progression, and pain severity. Future multicenter studies with larger sample sizes, inclusion of early-stage disease and control groups, standardized sampling according to menstrual cycle phase, and more detailed pain phenotyping are needed to further clarify the clinical utility of TNF-α and CA125 in endometriosis assessment.

Conclusion

TNF-α and CA125 showed different associations with endometriosis severity and pain severity. CA125 demonstrated a significant positive correlation with rASRM disease severity and better discriminative ability for distinguishing stage IV from stage III disease. In contrast, TNF-α was not significantly associated with disease severity. Both TNF-α and CA125 showed significant positive correlations with pain severity based on NRS classification. However, their ability to discriminate severe pain (NRS ≥7) was only fair, indicating limited utility in stratifying pain severity. Overall, CA125 appears to be more consistently associated with disease severity than TNF-α, while both biomarkers show only modest value in distinguishing pain severity. These findings support their role as adjunct markers for severity assessment rather than standalone clinical decision tools.

Ethics approval

The study protocol was reviewed and approved by the Ethics Committee of the Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (Approval No.386/ETIK-RSUDZA/2025).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study utilized artificial intelligence (AI) tools, ChatGPT and QuillBot, to improve grammar, sentence structure, and readability. The authors critically reviewed and revised all AI-generated outputs to ensure accuracy, coherence, and alignment with the study's objectives. The final decisions, interpretations, and manuscript content reflect the authors' independent judgment and intellectual contributions.

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